REMARKS

I. Remarks and Amendments

The Examiner indicated that the reference, cited as C33 in the information disclosure statement (IDS) as the International Search Report for International Application No. PCT/US2004/031704, has not been considered. The Examiner further explained the requirements under 37 C.F.R. § 1.98(a)(2) and stated that the references cited in the Search Report have not been considered. Office Action at page 2. The Applicants would like to clarify for the record that each of the references cited in the Search Report (C33) are listed independently on the IDS submitted by the Applicants (*see* B30-33 and C23-32), and the Examiner has marked them as considered.

Claims 1-16 are currently pending. Claims 1-7 and 9-16 are under examination and remain variously rejected under 35 U.S.C. § 102(b); §112, first paragraph, (written description and enablement; and §112, second paragraph. Claims 5, 9, and 10 are amended herein. Claims 13, 15, and 16 are canceled herein. Claims 17-19 are added herein.

Claim 5 is amended to remove reference to specific interleukins and neurotrophic factor. Specific interleukins are now recited in new claim 19 which depends from claim 5.

Claim 9 is amended to correct a typographical error from the previous amendment when the word "occlusion" was inadvertently omitted from the claim.

Claim 10 is amended to recite that the claimed method both reduces and prevents tissue damage. Support for this amendment is found throughout the specification and at least at page 1, lines 5-7.

Support for new claim 17 is found in the specification at least at page 19, lines 9-11 and 29-32.

Support for new claim 18 is found in the specification at least at page 3, lines 4-8; at page 5, lines 17-19; and at page 9, lines 7-8.

Support for new claim 19 is found in original claims 5 and 8, and in the specification at least at page 4, lines 21-25; at page 6, lines 8-12; and at page 11, lines 17-30.

No new matter is introduced by the amendment to the claims. Support for the amendments is found throughout the specification and the original claims as filed.

The Applicants do not intend, with these or any other amendments, to abandon the subject matter of claims previously presented, and reserve the right to pursue such subject matter in duly filed continuing patent applications.

II. Patentability Arguments

A. The Rejections under 35 U.S.C. §102(b) May Properly Be Withdrawn.

1. Orlic does not anticipate the subject matter of any pending claim.

The Examiner maintained the rejection of claims 1, 2, and 9 under 35 U.S.C. § 102(b) for anticipation by Orlic et al., *Proc. Natl. Acad. Sci.* 98:10344-10349, 2001 (hereinafter "Orlic"), because Orlic assertedly discloses the administration of a composition comprising G-CSF three days following coronary artery ligation, in addition to five days preceding coronary artery ligation, demonstrating that this composition was given following ischemia and not merely prophylactically. Thus, the Examiner asserted that the additional steps taught by Orlic are not limiting as applied to the instant claims, because as long as Orlic teaches each of the steps of the instant claimed methods their disclosure anticipates the claimed methods herein. Office Action at pages 6-7. The Examiner also rejected claims 11-16 under 35 U.S.C. §102(b) as anticipated by Orlic as evidenced by Gottlieb et al. (*Ann. N.Y. Acad. Sci.* 874: 412-426, 1999; hereinafter "Gottlieb"). The Examiner reasoned that the claims recite improvements in a method of reperfusion therapy where the reduction in damage is characterized by improvement in cardiac function, reduced scarring of the myocardium, reduction in cardiomyocyte apoptosis, reduction in necrosis, regeneration of the myocardium, and neoangiogenesis in the infarct zone. The Examiner asserted that Orlic discloses an improvement in cardiac function of mice after infarct-related myocardial tissue damage and treatment with G-CSF, myocardial regeneration after infarct-related myocardial tissue damage and treatment with G-CSF, reduced scarring of the myocardium after treatment with G-CSF, and neoangiogenesis in the infarcted zone after infarct-related myocardial tissue damage and treatment with G-CSF. Gottlieb was cited for assertedly disclosing that necrosis and apoptosis are inherent properties of scarring. Office Action at pages 9-10. In response, the Applicants disagree.

The pending claims recite a method consisting of a single step which is distinct from the method disclosed in Orlic. The transitional phrase "consisting of" excludes

any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("consisting of" defined as "closing the claim to the inclusion of materials other than those recited except for impurities ordinarily associated therewith."). M.P.E.P. § 2111.03. Consequently, a claimed method "consisting" of expressly recited steps cannot be anticipated by a method disclosed in the prior art that includes steps other than those expressly recited in the claimed method.

Orlic showed that the mobilization of primitive bone marrow cells prior to acute myocardial infarction, resulted in tissue regeneration in the ischemic site. In Orlic's two step method, SCF and G-CSF were co-administered daily for five days prior to induced infarction (coronary artery ligation), and then co-administered daily for three days after the ischemic event. Thus, Orlic's treatment method contains a prophylactic step prior to an ischemic event that is not recited in any of the rejected claims.

Unlike Orlic, the present invention contemplates an effective treatment for acute myocardial infarction or arterial occlusion *after, and only after,* an ischemic event has occurred. There is no step involving treatment *prior to* an ischemic event. Accordingly, the rejected claims cannot read on Orlic's disclosed method.

The difference between the two methods is significant. For example, Orlic's method requires administration *prior* to an ischemic event. The usefulness of this methods therefore premised on being able to predict that an ischemic event *will* occur, and also *when* such an event will occur with at least some degree of accuracy in order to achieve the desired result. In the method of the present claims, one of skill in the art need only know that an ischemic event *has* occurred; no prediction is required.

As for other differences, it is also noted that Orlic's method required administration of both SCF and G-CSF to increase the number of circulating stem cells (*see* page 10344, column 2). In fact, Orlic attributed most of the success of their treatment to the role of SCF (*see* page 10349, column 1) by postulating that "SCF could be responsible for migration, accumulation, and multiplication of primitive BMC in the infarcted zone where they acquire the heart muscle phenotype reaching functional competence."

Thus, the method of Orlic requires a step in the treatment of acute myocardial infarction that is not recited in the rejected claims and is expressly excluded by recitation of closed transitional language in the claims. Accordingly, the disclosure of Orlic cannot

anticipate the subject matter of claims 1, 2, or 9. Because the Orlic disclosure is immaterial to the claimed invention, the disclosure of Gottlieb has no relevance.

2. Anversa does not anticipate the subject matter of any pending claim.

The Examiner maintained the rejection of claims 1-7 and 9-10 under 35 U.S.C. §102(b) as assertedly anticipated by the disclosure of Anversa, (Pre-grant Patent Publication No. US 2002/0061587 A1 [05/2002]; hereinafter "Anversa") for reasons of record in the Office Actions of March 22, 2005 and October 20, 2004. The Examiner also asserted that: 1) Anversa discloses the administration of cytokines, including G-CSF, for the treatment of infarct-related myocardial tissue damage (page 1, paragraph [006]); 2) Anversa's methods to restore cardiac function take advantage of the regenerative properties of stem cells and cytokines (page 1, paragraph [0003]; and page 2, paragraph [0022], respectively); 3) Anversa's methods are also drawn to treating cardiovascular diseases, including ischemia, and define ischemic events as encompassing clinical scenarios such as bypass surgery (page 1, paragraph [0003]; and page 2, paragraph [0014], respectively); and 4) Anversa stated that the administration of cytokines, including G-CSF, following ischemia involves neoangiogenesis and restores "structural and functional integrity to the infarcted area" (page 3, paragraph [0038]; and page 4, paragraph [0044]). The Examiner concluded that as long as Anversa teaches each of the steps of the instant claimed methods, Anversa's teachings fully encompass the claimed methods. Office Action at page 7.

The Examiner also rejected claims 11-16 under 35 U.S.C. §102(b) as assertedly anticipated by the disclosure of Anversa. The Examiner reasoned that the claims recite improvements in a method of reperfusion therapy where the reduction in damage is characterized by improvement in cardiac function, reduced scarring of the myocardium, reduction in cardiomyocyte apoptosis, reduction in necrosis, regeneration of the myocardium, and neoangiogenesis in the infarct zone. The Examiner asserted that 1) Anversa discloses that the administration of cytokines, including G-CSF, for the treatment of myocardial tissue damage; 2) the methods of Anversa are drawn to treating cardiovascular diseases, including ischemia, and the methods take advantage of the regenerative properties of stem cells and cytokines; and 3) the administration of cytokines following ischemia involves neoangiogenesis. Moreover, Anversa assertedly discusses myocardial regeneration and

reduced scar formation in cytokine-treated mice. Office Action at pages 9-10. In response, the Applicants traverse the rejections.

The Applicants submit that Anversa's methods to restore cardiac function take advantage of the regenerative properties of stem cells and cytokines; however, the Applicants contend that Anversa's methods rely principally on the implanting, depositing, or administering of stem cells (*see* page 1, paragraph [006]). Anversa's methods are also drawn to treating cardiovascular diseases, including ischemia, and define ischemic events as encompassing clinical scenarios such as bypass surgery (page 1, paragraph [0003]; and page 2, paragraph [0014], respectively). For clarification, the Applicants submit that, contrary to the Examiner's assertion, Anversa did not state, at page 3, paragraph [0038], and page 4, paragraph [0044], that the administration of G-CSF following ischemia involves neoangiogenesis and restores structural and functional integrity to the infarcted area. Instead, Anversa, at paragraph [0038], discusses that the administration of a "cytokine" to a patient stimulates the patient's own stem cells to migrate to damaged tissue and restore functional integrity; however, Anversa does not specify which "cytokine" should be administered or when the "cytokine" should be administered.

Despite the Examiner's characterization of the disclosure of Anversa, the Applicants submit that this disclosure does not enable the presently claimed methods and thus cannot anticipate the claimed subject matter. When the Patent Office cites prior art as being anticipatory, an applicant can overcome the rejection "by proving that the relevant disclosures of the prior art . . . are not enabled." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). The enablement requirement of 35 U.S.C. § 112, first paragraph, ensures that an application teaches how to make and use the invention as claimed without requiring undue experimentation. The inquiry may be guided by consideration of several factors enumerated in a biotechnology context. *In re Wands* 858 F.2d 731 (Fed. Cir. 1988). In *Wands*, the Federal Circuit set forth a number of factors which a court may consider in determining whether a disclosure would require "undue" experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands* 858 F.2d 731, 737. However, all of the *Wands* factors need not be reviewed when determining whether a disclosure is enabling.

Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1213 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts."). The Applicants submit that applying the "*Wands*" analysis to the disclosure of Anversa can only lead to the conclusion that the cited reference does not enable one of ordinary skill in the art to practice the presently claimed invention without undue experimentation.

The nature of the invention, as discussed throughout the specification and as recited in the claims, is a method for treating acute myocardial infarction in a mammal to reduce-infarct related myocardial tissue damage.

In arts such as biotechnology, enablement requires more extensive disclosure because of the unpredictability involved in practicing inventions in these arts. *See* generally *Chisum on Patents*, § 7.03[4][d][i], at 7-58 (1999) ("A recurring problem is whether a specification that sets forth a single or a limited number of examples can be enabling of broad claims when the subject matter concerns biological materials or reactions, which are generally considered to be unpredictable.") and cases cited therein; *Ex parte Hitzeman*, 9 U.S.P.Q.2d 1821 (Bd. Pat. App. Interf. 1988) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more is required . . . ."); *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The amount of guidance presented and the presence or absence of working examples are two additional factors relevant to enablement. Anversa does not provide any guidance regarding the administration of a "cytokine" alone *after and only after* a myocardial infarction. There is no mention of (1) when to begin cytokine treatment after an infarction; (2) what cytokine(s) to use and if any are effective alone; and (3) the beneficial effects of this post-MI only treatment. Instead, Anversa provides guidance as how to administer SCF along with G-CSF *both prior to and after* the occurrence of a myocardial infarction as in Orlic discussed above. Furthermore, Anversa does not provide any working examples, either actual or prophetic, which demonstrate that cytokines administered *after and only after* a myocardial infarction has already occurred have any therapeutic effect. More specifically, there is no example of using G-CSF alone post-MI to have a therapeutic effect.

Consequently, the Applicants submit that the disclosure of Anversa does not anticipate the claimed subject matter. At a minimum, Anversa is defective as an anticipatory reference because Anversa specifically states that their methods, compositions, and kits for

repairing damaged myocardium and/or myocardial cells includes "the administration of stem cells, such as adult stem cells, optionally with cytokines" (*see* Abstract on the title page). Anversa's methods comprise the delivery of somatic stem cells, alone or in combination, with cytokines, including SCF, G-CSF, GM-CSF, IL-3, etc. (*see* Anversa at paragraphs [005 and 0044]). In fact, Anversa never discloses the treatment of mammals with G-CSF in conjunction with reperfusion therapy after myocardial infarction to reduce heart damage (*see* Anversa's Examples 1-7; paragraphs [0160-0201]. Anversa's Example 2, for example, uses only the prophylactic treatment of SCF in combination with G-CSF for five days prior to an induced acute myocardial infarction to improve survival, promote myocardial regeneration, reduce infarct size, and increase posterior wall thickness (same results as published by Orlic as discussed above). Anversa did not disclose the use of G-CSF in a reperfusion therapy method for improved patient outcome or increased ventricular wall thickness.

To the extent that Anversa discloses any cytokine therapy relating to MI, the disclosure provides the worker of ordinary skill with little more than an invitation to experiment. The broad statements of some undefined therapeutic method do not provide any guidance as how to practice a method within the scope of the broad statement. "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Id* at 1366.

The Applicants therefore submit that the absence in the Anversa disclosure of any specifics with regard to carrying out the methods of the present claims precludes any assertion that the disclosure enables a worker of ordinary skill in the art to carry out the invention as claimed. Accordingly, Anversa cannot anticipate independent claims 1, 9, or 10.

As set out in Section II A I above, a dependent claim incorporates each limitation of a claim from which it depends. Thus, claims 2-7 depend from claim 1 and, as established above, Anversa cannot anticipate the subject matter of the broad claim. Necessarily then, Anversa cannot anticipate any claim which depends from claim 1.

B. The Rejections Under 35 U.S.C. §112, First Paragraph, May Properly Be Withdrawn.

1. Written Description

The Examiner rejected claims 11-16 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement for representing new matter that is not described in the specification. The Examiner asserted that claims 11-16 recite the method of claim 1 wherein the reduction in damage is characterized by an improvement in cardiac function, reduced scarring of the myocardium, reduced cardiomyocyte apoptosis, reduced necrosis, regeneration of the myocardium, and induced neoangiogenesis of the infarcted zone. The Examiner also asserted that the teachings of Kocher et al. (*Nature Med.* 7: 430-436, 2001; *see* specification at page 6, lines 14-19; hereinafter "Kocher") in a rat model of MI demonstrated that the injection of endothelial cell precursors, mobilized by G-CSF, induced neoangiogenesis in the infarcted zone, prevented cardiomyocyte apoptosis, reduced scar formation, and improved ventricular function. Although the Examiner realized that the methodologies of Kocher are different than the claimed subject matter, the Examiner asserted that claims 11-16 represent new matter that is not described in the specification. Office Action at pages 7-8.

In response, the Applicants respectfully traverse this rejection and submit that claims 11-16 find written descriptive support in the originally filed disclosure. Moreover, this new matter rejection is now moot in consideration of the amendments to the claims.

To comply with the written description requirement of 35 U.S.C. § 112, first paragraph, each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. *See* M.P.E.P. § 2163.05. Claim 11 finds support in the specification at least at page 19, lines 9-13; and at page 20, lines 14-17. Specifically, the specification teaches that the invention contemplates that treatment with G-CSF improves cardiac function, and the specification provides experiments for determining the critical time period at which treatment with G-CSF improves cardiac function.

Claim 12 finds support in the specification at least at page 1, lines 16-18; and at page 9, lines 5-7 and 12-14. Therein, the specification teaches that the invention contemplates that the loss of blood flow from occlusion of the artery to the heart causes

scarring, and the subsequent expedient restoration of blood flow will reduce damage. Consequently, the subsequent expedient restoration of blood flow will reduce scarring. Furthermore, the specification recites that reperfusion therapy provides relief to the damaged tissue and inhibits further scarring of the myocardium. Thus, it logically follows that there will be reduced scarring in an improved reperfusion therapy method which reduces infarct-related myocardial tissue damage.

Claim 14 finds support in the specification at least at page 1, lines 18-19; and at page 9, lines 4-11. Therein, the specification teaches that the loss of blood flow causes necrosis and reperfusion therapy restores blood flow. As set out above, it logically follows that there will be reduced necrosis in an improved reperfusion therapy method which reduces tissue damage. The specification also discusses the disclosure of Kocher at page 6, lines 14-19, which implicates G-CSF as having a role on bone marrow cells in inducing neoangiogenesis in the infarcted zone; preventing cardiomyocyte apoptosis; reducing scar formation; and improving ventricular function.

Claims 13, 15, and 16 are canceled by amendment.

New claim 17 finds support in the original specification at least at page 19, lines 9-11 and 29-32, which teaches that cardiac wall thickness loss was measured by a change in mean infarct thickness, and was found to be -3.0 ± 0.9 in pigs in the early treatment group compared to -4.5 ± 0.5 in the controls. Thus, wall thickness loss was reduced by early treatment with G-CSF.

New claim 18 finds support in the original specification at least at page 3, lines 4-8; at page 5, lines 17-19; and at page 9, lines 7-8. Specifically, the specification teaches that treatment using the claimed methods will improve patient outcome.

New claim 19 finds support in original claims 5 and 8, and in the specification at least at page 4, lines 21-25; at page 6, lines 8-12; and at page 11, lines 17-30.

In view of the foregoing comments and the amendments, the rejection of claims under 35 U.S.C. § 112, first paragraph, for asserted lack of written description must be withdrawn.

2. Enablement

The Examiner indicated that the rejection of claims 1 and 5 under 35 U.S.C. §112, first paragraph (enablement), was maintained for reasons of record; however, the Examiner did not address the amendment to claim 1 or the Applicants' arguments provided in the response filed May 20, 2005 as they relate to the enablement of claim 1. In the previous Office Action, the Examiner asserted that the specification, while being enabling for a method of improving wall thickness following ischemia and reperfusion, does not assertedly provide enablement for the broad claim of a method of reducing all forms of heart damage following ischemia and reperfusion. The Applicants previously amended the claims to specify that the form of heart damage addressed in the claimed subject matter is infarct-related myocardial tissue damage. Accordingly, the Applicants request clarification, explanation, or withdrawal of the rejection for lack of enablement as it relates to claim 1. Office Action at page 3.

Claims 2-4, 6, 7, 9, and 10 were also rejected under 35 U.S.C. §112, first paragraph (enablement), for the reasons of record and the reasons set out below. Claim 2 was rejected because, although the specification teaches that G-CSF promotes myocardial repair by improving wall thickness in the infarct zone, the Examiner asserted it does not teach the use of G-CSF for reducing wall thickness losses. Claim 10 was rejected because, while the specification may be enabling for an improvement in a method of bypass surgery that reduces tissue damage consisting of administering an effective amount of a composition comprising G-CSF, the Examiner asserted that it does not reasonably provide enablement for a method of bypass surgery that would reduce tissue damage. Claims 3, 4, 6, and 7 were apparently rejected for depending from claim 1 although no reason is provided in the action. Likewise, no reason for rejecting claim 9 for an asserted lack of enablement is provided in the Office Action. Office Action at pages 3-5. In response, the Applicants respectfully traverse the rejections.

It is a well known tenet of the law that a specification disclosure need not teach, and preferably should omit, what is well known to those of skill in the art. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). As long as the specification contains at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claimed invention, then the enablement requirement

under 35 U.S.C. §112 is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA, 1970); MPEP § 2164.01(b).

The Examiner rejected claim 2 because the specification does not assertedly provide enablement for the use of G-CSF for reducing wall thickness losses in the heart after an infarct. The Examiner went on to assert that there is cardiomyocyte hypertrophy after an infarct which results in myocyte cell thickening (Melillo et al, *Circulation* 93: 1447-1458, 1996), and ultimately results in cardiac wall thickening. The Examiner then drew the unsubstantiated conclusion that a reduction in wall thickness losses can only result from preventing or decreasing cardiac damage before or during an infarct, and since the claims are drawn to treatment after an AMI has occurred, a reduction in wall thickness loss cannot be made within the scope of the disclosure Office Action at pages 3-4. The Applicants respectfully disagree.

Example 1 states that all animals underwent cardiac magnetic resonance imaging (MRI) including cine-MR and contrast enhanced MR at five days (Scan 1) and 56 days (Scan 2) days post AMI. Myocardial infarct thickness was calculated as average thickness from three short axis views in the area of maximum infarction. Change in mean infarct thickness was measured as the difference in mean infarct thickness between Scan 2 and Scan 1 (e.g., mean infarct thickness of Scan 2 minus (–) mean infarct thickness of Scan 1). Pigs in the early treatment group demonstrated a significant difference (P=0.01) in mean infarct thickness (-3.0 ± 0.9 mm) compared to controls (-4.5 ± 0.5 mm). Thus, one of skill in the art would conclude that there was a reduction in wall thickness loss in pigs in the early treatment group with the early treatment group only losing an average of 3.0 mm (-3.0 ± 0.9 mm) compared to a loss of 4.5 mm (-4.5 ± 0.5 mm) in the delayed treatment group. The Applicants submit that this is just another way of saying the same thing, and this is not a "hypertrophy" of the cells of the heart or a thickening of the walls of the heart as the Examiner suggests. Scan 2 (at day 56) obviously showed a decrease in mean infarct thickness compared to Scan 1 (at day 5) to result in the negative numbers provided above and in the originally filed specification. If there were such a hypertrophy, one of skill would expect the second scan to have a greater mean infarct thickness than the first scan, which would result in a positive number. Thus, there is no support in the specification for such an allegation by the Examiner. Consequently, G-CSF treatment reduced wall thickness loss and the rejection on this basis should be withdrawn.

The Examiner maintained the rejection of claim 5 for lack of enablement for assertedly not fully enabling the administration of IL-8 or other pro-inflammatory cytokines, including neurotrophic factors (as listed in claim 5), to reduce infarct-related myocardial tissue damage. The Applicants respectfully traverse for reasons of record. Moreover, the basis alleged for this rejection is now moot in consideration of the amendments to the claims.

Solely to expedite prosecution, the Applicants have amended claim 5 to remove reference to IL-8 and neurotrophic factor and to render moot the rejection of claim 5 for lack of enablement.

The Examiner rejected claim 10 for assertedly not providing enablement for a method of bypass surgery that would reduce tissue damage. The Applicants disagree because one skilled in the art knows that bypass surgery reroutes, or "bypasses," blood around clogged arteries to improve blood flow and oxygen to the heart (*see* Appendix A; "What is Coronary Bypass Surgery?," published by the American Heart Association; document may be downloaded online @ www.american.heart.org). The surgery in itself is another method of reperfusing the heart with more blood and consequently more oxygen. Accordingly, the administration of G-CSF in conjunction with bypass surgery will reduce tissue damage to the already oxygen-deprived heart and prevent future tissue damage by allowing more blood to circulate through the heart. Moreover, one skilled in the art knows that the interruption of the flow of blood during bypass surgery leads to ischemia (*see* Anversa at paragraph [0014]), which may affect cardiovascular tissue and cause tissue damage. Consequently, the rejection of claim 10 for lack of enablement should be withdrawn.

In view of the foregoing comments and the amendments to the claims, the Applicants submit that claims 1-7, 9, and 10 are fully enabled by the present specification and the rejection of the claims under 35 U.S.C. § 112, first paragraph, should be withdrawn.

C. The Rejection Under 35 U.S.C. § 112, Second Paragraph, May Properly Be Withdrawn.

The Examiner rejected claims 1-7, 9, and 11-16 under 35 U.S.C. §112, second paragraph, assertedly because the phrase "administration before, concurrently with, and/or after reperfusion therapy" renders the claim indefinite because it extends the method outside the reperfusion therapy. Office Action at page 8. The Examiner rejected claim 10 under 35

U.S.C. §112, second paragraph, assertedly because the phrase "administration before, concurrently with, and/or after bypass surgery" renders the claim indefinite because it extends the method outside the bypass surgery. Office Action at page 9. The Examiner also rejected claim 5 under 35 U.S.C. §112, second paragraph, assertedly because claim 5 recites both the broader genus of "interleukins" and the individual species of interleukins (e.g., "IL-1, IL-2," etc.) which are narrower in range/limitation. Office Action at page 9. In response, the Applicants respectfully traverse the rejections.

The specification provides that G-CSF may be administered after an AMI but either before, concurrently with, and/or after the reperfusion (*see* specification at page 12, lines 3-7). The Applicants submit, however, that this phrase does not make the claim indefinite and the method is fully supported by the specification. For example, the specification discusses that G-CSF treatment is given in conjunction with reperfusion therapy (*see* specification at least at page 1, lines 4-8; at page 3, lines 4-8; at page 5, lines 23-25 and 29-30; at page 8, lines 2-4; and at page 9, lines 20-22). The specification also explains that reperfusion therapy for the treatment of AMI consists of primary angioplasty and/or administration of a thrombolytic agent, which can be accomplished mechanically, with primary balloon angioplasty or stenting, or medically, with a thrombolytic agent. The specification also teaches that the reperfusion can be performed surgically, as with bypass surgery. Thus, it will be readily appreciated that the G-CSF polypeptide could be administered before, concurrently with, and/or after the mechanical, medical, or surgical method used in performing the reperfusion and still be considered to be a part of the method of reperfusion therapy.

As explained above, bypass surgery is one means of reperfusion therapy. Thus, it will be appreciated that the G-CSF polypeptide could be administered before, concurrently with, and/or after the surgical method, i.e., bypass surgery, used in performing the reperfusion and still be considered to be a part of the method of bypass surgery.

Moreover, the rejection of claim 5 for indefiniteness is now moot in view of the amendment to said claim. Claim 5 has been amended to remove the individual species of interleukins from the claim. New dependent claim 19 has been added to recite the individual species of interleukins contemplated for use in the invention.

In view of the discussion provided above, the Applicants respectfully submit that the rejections of claims under section 112, second paragraph, must be withdrawn.

III. Conclusion

In view of the above, the Applicants respectfully submit that the claims are in condition for allowance and respectfully request expedited notification of same. Should the Examiner have any questions, she is welcomed to contact the undersigned at the telephone number below.

Respectfully submitted,

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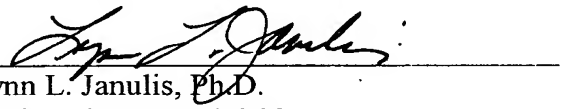
By: 

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